CASE REPORT

Unusual cause of chest pain: empyema necessitans and tubercular osteomyelitis of the rib in an immunocompetent man

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SUMMARY

A 33-year-old man, born in India but resident in the UK for 5 years, presented to the emergency department with a 4-week history of a dry cough and right-sided pleuritic chest pain. He reported systemic features, including fever and unintentional weight loss. His medical history included vitamin D deficiency. He had travelled to India 10 months previously and denied any exposure to tuberculosis (TB). He was an ex-smoker with a 20 pack history. Respiratory examination confirmed decreased air entry of the right lower lobe and stony dullness on percussion. His C reactive protein was 178 mg/L. A chest radiograph identified a moderate-sized right-sided pleural effusion and destruction of the lateral aspect of the right fifth rib, strongly suggestive of underlying malignancy. Further investigation with a CT of the thorax identified a focal lytic lesion in the right fifth rib, at its lateral aspect, with expansion of the rib observed. Ultrasound-guided pleural aspiration confirmed an exudative pleural effusion. Gram stain revealed no organisms or polymorphs. Four days post admission, the patient was transferred to the regional thoracic surgery unit and underwent video-assisted thoracic surgery, bronchoscopy and drainage of his empyema. His Mantoux tuberculin skin test and his TB Elispot were negative, suggesting that TB infection was unlikely. Culture confirmed no growth after 48 h incubation. Histology of his pleural biopsy identified multiple non-confluent necrotising granulomatous inflammation with very occasional acid-alcohol-fast bacilli-like organisms, highly suspicious for mycobacterial infection. The isolate, *Mycobacterium tuberculosis*, was identified by Accuprobe and HAIN tests, respectively. MPT64 erythrocyte sedimentation rate (ESR) results from the fifth rib were positive for *M. tuberculosis*. This case report discusses the aetiology, clinical presentation and pathophysiology of both empyema necessitans and tubercular osteomyelitis of the rib.

BACKGROUND

Empyema necessitans is a rare complication of untreated pleural space infections and most cases are related to *Mycobacterium tuberculosis*. Tuberculous infection of the thoracic cage is a rare clinical entity and is difficult to discern clinically or radiographically, thus requiring a high degree of suspicion for accurate and timely diagnosis. Tuberculosis (TB) of the skeleton comprises 10–15% of all extrapulmonary TB cases, but involvement of the rib is rare.

Therefore, we report our experience of successfully treating a 33-year-old immunocompetent man

following the diagnosis of empyema necessitans and tubercular osteomyelitis of the rib, with video-assisted thoracic surgery (VATS) and antitubercular therapy. This rare case report focuses on both pathologies, and the importance of bacteriological and histopathological confirmation of the disease is stressed.

CASE PRESENTATION

A 33-year-old man, an IT professional born in India but resident in the UK for 5 years, presented to the emergency department (ED) with a 2-month history of general malaise. He reported a 4-month history of right-sided pleuritic chest pain and a 4-week history of a dry cough. Associated symptoms included fever, night sweats, loss of appetite and unintentional weight loss (3 kg over 4 weeks). He had no significant medical history apart from vitamin D deficiency. He had, 4 months previously, presented to the ED, with right-sided chest pain; his chest X-ray was normal. He had travelled to India 10 months earlier and denied exposure to TB. He was an ex-smoker with a 20 pack history, and did not consume alcohol.

On presentation, he was febrile with a temperature of 38.9°C, heart rate 118 bpm, blood pressure 119/72 mm Hg, respiratory rate 14 breaths/min and oxygen saturation 96% on room air. Clinical examination revealed a BCG scar on his right deltoid. Respiratory examination confirmed decreased breath sounds and vocal fremitus in the right lower lobe, stony dullness on percussion and tenderness over his right lateral chest wall. The rest of his systemic examination was unremarkable.

INVESTIGATIONS

Haematological investigations confirmed a white cell count of $8.5 \times 10^9/L$ and C reactive protein 178 mg/L. Renal and liver function tests were unremarkable. In addition, no serological evidence of hepatitis C infection or HIV was observed. A 12-lead ECG revealed no dynamic change. A chest radiograph identified a moderate-sized right-sided pleural effusion with destruction of the right fifth rib (figure 1). The autoimmune screen was negative. Blood cultures isolated Gram-positive cocci, resembling *Streptococcus sanguinis*.

TREATMENT

Ultrasound-guided pleural aspiration was performed and 500 ml of straw-coloured fluid was aspirated and sent for analysis. This was an

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Figure 1 Chest radiograph. A moderate-sized right pleural effusion and airspace opacification adjacent to the right hilum was noted. The mediastinum remains central, indicating some collapse in the underlying lung. The left lung was clear. There was destruction of the lateral aspect of the right fifth rib.

exudative pleural effusion and Gram stain of the pleural fluid revealed no organisms or polymorphs. Culture confirmed no growth after 48 h incubation and no fungal growth after 4 weeks. Pleural fluid cytology showed an increased number of lymphocytes and scattered reactive mesothelial cells, but no malignant cells were seen. Further investigation with a chest CT showed consolidation in the middle lobe and right lower lobes, with an associated right-sided pleural effusion (figure 2). The pleura was thickened (6 mm) and the effusion was suspicious of an empyema. A focal lytic lesion was noted in the right fifth rib, raising the possibility of osteomyelitis or tumour (figure 3). Four days post admission, the patient was transferred to the regional thoracic unit, and underwent right-sided VATS and drainage of his empyema. He was transferred back to the Respiratory Ward at Milton Keynes University Hospital 10 days later, with a chest drain and an ambulatory drain bag, with follow-up scheduled in the drain clinic 5 days later. He was prescribed ciprofloxacin 750 mg two times per day for 14 days

Figure 2 CT of the thorax, with contrast. There was consolidation in the right lung and a moderate/large right hydropneumothorax was noted. There was pleural thickening, suspicious for empyema.

Figure 3 CT of the thorax, with contrast. There was also a focal lytic lesion in the right fifth rib, with associated soft tissue thickening at its periphery. The nature of this lesion was uncertain. Appearances were not typical for a fracture and raised the possibility of tumour or osteomyelitis.

postoperatively. His Mantoux tuberculin test and TB Elispot were both negative, suggesting that tuberculous infection was unlikely. Phenol Auramine Microscopy and the molecular amplification test of the right pleural tissue were negative for *M. tuberculosis* complex. However, the histology of the pleural biopsy identified multiple non-confluent necrotising granulomatous inflammations with very occasional acid-alcohol-fast bacilli-like organisms, highly suspicious for mycobacterial infection (figures 4 and 5). The isolate was further subjected to genotype assays (AccuProbe and HAIN test), which identified *M. tuberculosis*. Real-time PCR of the resected rib specimen, performed in the Microbiology Department at Great Ormond Street Hospital, was negative for both *Streptococcus pyogenes* and *Staphylococcus aureus*. *M. tuberculosis* DNA was detected, but non-tuberculous *Mycobacterium* spp DNA was not detected. Interestingly, ESAT-6, detected from BCG strains, was noted.

Therefore, this result indicated the presence of a non-BCG strain in this sample. MPT64 ESR results from the fifth rib were positive for *M. tuberculosis*.

OUTCOME AND FOLLOW-UP

The patient was started on quadruple therapy: rifampicin, isoniazid and pyrazinamide. In addition, he received vitamin D 20

Figure 4 Chest radiograph demonstrating resolution of the right-sided lung changes.

Figure 5 Lower power pleural biopsy (H&E×40). Pleural biopsies showing pleural fibrosis with abundant necrotising and non-necrotising epithelioid granulomas. Occasional acid-fast bacilli were identified in the granulomas on Ziehl-Neelsen stain, confirming mycobacterial infection.

000 units weekly to correct his deficiency, and pyridoxine 10 mg once daily. Baseline bloods were performed (liver function tests were normal) and he also underwent baseline visual acuity and colour vision assessment. As TB is a notifiable disease, infection control measures were required and the Consultant for Communicable Disease Control was informed. The patient was reviewed 2 weeks post discharge in the respiratory clinic and remained asymptomatic, with no systemic features reported. He is currently receiving treatment with rifampicin and isoniazid. He remains under review in the respiratory department and his latest chest radiograph revealed resolution of his right-sided lung changes (figure 6).

DISCUSSION

TB was declared a global emergency by the WHO, in 1993, and it remains one of the world's deadliest communicable diseases, with high mortality and morbidity reported. According to the WHO Global Tuberculosis Report, in 2013, an estimated 9 million people developed TB and 1.5 million died from the disease, 360 000 of whom were HIV positive.¹ The rate of TB in the UK has remained high but relatively stable over the last

Figure 6 High-power image of pleural biopsy (H&E×200). The pleural biopsies showing pleural fibrosis with necrotising and non-necrotising granulomas. Occasional acid-fast bacilli were identified.

decade, with the overall incidence currently at a similar level to that in 2003. In 2013, in the UK, a total of 7892 cases of TB were notified, a rate of 12.3 cases/100 000 population.¹ Since the advent of 23 cases of TB of the ribs, described by Tatelman and Drouillard² there has been a relative dearth of cases in the literature. Up until 2004, only 6 cases of TB of the thoracic wall involving the ribs were reported.^{3–7} Rasool,⁸ in his study of 42 children with tubercular osteomyelitis, found an incidence of 20% with chest involvement. Bone and joint TB classically affects the weight-bearing joints, such as the knees and those of the hip, and is usually monoarticular in nature. It appears to be common in HIV-infected individuals or intravenous drug users. Faure *et al*⁹ stated that tubercular abscesses of the chest wall are most frequently found at the margins of the sternum and along the rib shafts. Interestingly, according to Mulloy,¹⁰ tuberculous osteomyelitis has been associated with the BCG vaccination, as in our case.

Empyema necessitans, a rare complication of untreated pleural space infections leading to spontaneous eruption through the parietal pleura and subcutaneous abscess formation, was first described by Gulland De Baillon in 1640, when it developed after the spontaneous eruption of a syphilitic aneurysm. In 1940, Sindel published the last comprehensive review, summarising 112 cases worldwide, with 84 cases caused by TB. Owing to the advent of antibiotics and the earlier detection and treatment of pneumonia and parapneumonic effusions, empyema necessitans is now a rare clinical entity.¹¹ In the preantibiotics era, mortality was as high as 87%, with most cases caused by *M. tuberculosis*, *Streptococcus pneumoniae*, *S. aureus*, *S. milleri*, *Pseudomonas cepacia* and *Mycobacterium avium* intracellularly. Empyema necessitans may be asymptomatic, but it can also present with pleuritic chest pain, a non-productive cough and an enlarging soft tissue mass on the anterior chest wall. Indeed, it is also a rare cause of a pleural effusion. Osteomyelitis of the ribs can lead to empyema formation through the direct extension of infection. As in our patient, clinical manifestations of tubercular osteomyelitis present in an indolent manner, with a mean of 9.3 months and a range of 2 months to 6 years before a diagnosis is rendered. There is a male predominance, with a mean age of 36 years and non-specific symptoms including weight loss, night sweats, general malaise and loss of appetite. The most common presenting symptom includes local pain without pulmonary symptoms (<50% have active pulmonary disease) and an associated soft tissue swelling (81%). A non-healing sinus may also be present in more advanced cases. The most common site of extension is the anterior chest wall because the posterior lung is more adherent, and, less commonly, through the bronchus, breast, oesophagus, diaphragm, pericardium or the mediastinum.

Empyema can be classified as primary thoracic empyema, secondary to lung resection with or without bronchopleural fistula and secondary to trauma. Empyema evolves through three stages: exudative, fibropurulent and organisational. The exudative stage is characterised by clear, straw-coloured fluid, normal pH and glucose, with a lactate dehydrogenase (LDH) <500 U/L. The visceral pleura remains elastic and the thoracic dimensions remain unchanged.¹² In stage II, an increase in bacteria, leucocytes, debris and fibrin result in turbid and infected fluid, which becomes thick and purulent. Multiple loculations are created. The fluid pH is <7.2 and LDH>1000 U/L. The final stage occurs when the loculations are replaced by formal granulation tissue. The diagnosis of empyema is rendered by the presence of pus, a Gram-positive stain or culture of pleural fluid, or a pleural fluid pH <7.2 with a normal peripheral blood pH with

radiological features of empyema. CT is the most sensitive modality, with sonography in the evaluation of superficial masses a well-established diagnostic modality.

There are two major patterns of disease with TB. Primary infection, seen as an initial infection, is focused in the lung and caseous regional lymph node lesions. The initial focus of infection is a small subpleural granuloma accompanied by granulomatous hilar lymph node infection.

Together, these make up the 'Ghon complex', the characteristic macroscopic appearance. In nearly all cases, these granulomas resolve and there is no further spread of the infection.

Secondary TB is seen mostly in adults, as a reactivation of previous infection (or reinfection), particularly when health status declines. The granulomatous inflammation is much more florid and widespread. Typically, the upper lung lobes are most affected and cavitation can occur. When resistance to infection is particularly poor, a 'miliary' pattern of spread can occur in which there are a myriad of small millet seed-sized (1–3 mm) granulomas, either in the lungs or in other organs. Dissemination of TB outside of the lungs can lead to the appearance of a number of uncommon findings with characteristic patterns. The classic term 'scrofula', derived from the Latin word meaning 'brood sow', refers to cervical lymphadenitis, the most common extrapulmonary manifestation of TB. It may represent primary infection, spread from contiguous sites or reactivation. Multiplicity, matting and caseation are three important findings of tuberculous lymphadenitis.

Various aetiologies have been postulated to describe the pathophysiology of TB osteomyelitis, including reactivation of latent foci formed during haematogenous or lymphatic dissemination of primary TB. Robert Koch first described the tubercular bacillus during histopathological examination in 1885. A tuberculous rod is formed in the bone marrow with spread to the trabeculae, which are reabsorbed creating a lytic lesion. Destruction of bone results from pressure necrosis by granulation tissue and by the direct action of invading organisms. The granulation tissue may undergo caseation and liquefaction, thus creating an abscessed cavity with small granules of bone called 'sand bones'.¹³ Alternatively, it may become encapsulated by fibrous tissue, an 'encrypted tubercle'. Sometimes, the tuberculous granulation tissue spreads in the marrow and the trabeculae undergo erosion and absorption.

TB is considered the second commonest cause of rib destruction after metastasis from the breast or lung, but it is important to consider the differential diagnosis of a chest wall mass, including myeloma, lymphoma, eosinophilic granuloma, disseminated fungal or mycobacterial infection and sarcoma.² In children, lytic bone lesions may resemble other sinister pathologies, such as leukaemia, neuroblastoma and Langerhans cell histiocytosis.

Furthermore, how is the diagnosis of TB rendered? PCR analysis allows identification and genotyping of the *M. tuberculosis* complex demonstrating a good correlation with histological findings (85% sensitivity, 80% specificity). Owing to the increased incidence of multidrug-resistant TB, mycobacterial sensitivities on culture should always be assessed. Tuberculin skin testing may be helpful in primary diagnosis, but Mantoux and Heaf tests are more valuable in secondary disease. Variable acid–alcohol-fast bacilli positivity by Ziehl–Neelsen staining has been observed ranging from 0% to 77.8%. Interestingly, receipt of the BCG vaccine within the previous year has been associated with sternal osteomyelitis as a rare complication of the vaccine and has been noted to resolve after treatment with antituberculous medication. Clinical symptoms may precede radiological changes, which are varied, depending on the progression of

osteomyelitis, and include osteoporosis, osteopenia, bone lysis, sclerosis, periostitis or pathological fracture. The National Institute for Health and Care Excellence guidelines have suggested site-specific investigations for bone TB, including plain radiographs, CT, MRI, biopsy at the site of disease and cultures.

Indeed, the chest radiograph may be normal in 70% of cases. The radiographic and CT features of rib TB were aptly described by Morris as rib erosions and destruction with adjacent abscess formation.¹⁴ Recently, the role of positron emission tomography CT in the diagnosis of chest wall tubercular lesions has been discussed, with these lesions seen as areas of increased fluorodeoxyglucose uptake in active regions and granulomatous inflammation, with cold areas representing necrosed tissue.

TB of the rib is one such disease where preoperative tissue diagnosis may be difficult and it would be prudent to drain purulent collections by thoracotomy, decortication (for obliterating the cavity to prevent fibrosis and facilitate lung expansion) or wide surgical drainage, to confirm the diagnosis histopathologically and to initiate antitubercular therapy. And, what does the literature advocate? According to Reyes,¹⁵ empyema necessitans caused by *M. tuberculosis* has a cure rate of 99% when treated with isoniazid and rifampicin for 9–12 months. Mathlouthi states that surgery is rarely indicated and anti-TB therapy is all that is necessary once the diagnosis is confirmed by histology.¹⁶ However, Chang could only confirm TB in all of their 12 cases, following rib resection.¹⁷ Faure⁹ could not diagnose TB prior to surgery in many of their cases either. As well as this, Yao, in a large series of 712 cases, spanning 11 years, advocates surgical treatment for parietal chest wall TB.¹⁸ Agrawal is of the opinion that treatment for bone TB requires a minimum of 12 months of anti tubercular treatment and this is further reinforced in other Indian studies.^{19 20}

Learning points

- ▶ Primary tubercular osteomyelitis of the rib cage is a rare clinical entity and remains a diagnostic challenge for the clinician. It presents with clinical manifestations similar to other forms of osteoarticular tuberculosis (TB), including soft tissue swelling, which is the most common symptom, bone pain and swelling, erythaema, warmth and tenderness, enlarged regional lymph nodes, bone deformity or fracture, and a draining abscess or sinus.
- ▶ Clinical manifestations of TB of the rib present insidiously. Constitutional symptoms are less commonly seen, but include malaise, fever, night sweats and weight loss.
- ▶ Although there is no consensus guideline to the precise regimen and treatment duration for TB of the rib, antitubercular therapy is the mainstay of treatment. Many authors report surgical debridement to be essential to prevent recurrence or formation of a draining sinus.
- ▶ A history of recent TB contact should be sought as well as a log of travel to TB endemic regions. Homelessness, drug and alcohol abuse, malnutrition and immunosuppression should raise the clinical index of suspicion.
- ▶ Empyema necessitans is a rare complication of untreated pleural space infections and most cases are related to *Mycobacterium tuberculosis*. It may be asymptomatic, but can also present with pleuritic chest pain, a non-productive cough and an enlarging soft tissue mass on the anterior chest wall.

As already mentioned, primary tubercular osteomyelitis of the rib cage is a rare clinical entity and remains a diagnostic challenge for the clinician. A significant challenge in the diagnosis of TB osteomyelitis is that the smear for acid–alcohol-fast bacilli is often negative, leading to a delay in diagnosis.²¹ Indeed, a negative PCR, nucleic amplification assay, or a negative tuberculin skin test, found in 10% of cases, does not rule out the diagnosis of TB. The gold standard for diagnosis is the isolation of *M. tuberculosis* from cultures of bone biopsy specimens.²² Although chest wall TB and empyema necessitans are rare, they should be considered in an immunocompetent patient returning from an area of high endemicity for TB, presenting with a soft tissue chest wall mass and lytic rib lesions. As the presentation of extrapulmonary TB can be variable, it is important to maintain a high index of clinical suspicion, with a clinically directed multidisciplinary approach.

Competing interests None declared.

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